Office Action Summary	Application No.	Applicant(s)	
	10/583,795	NAKANO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,6,7,14-16,19-22,24-27,29,32,34,36-39,41 and 43-53* is/are pending in the application.

4a) Of the above claim(s) *19,20,24-27,43-46 and 48-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,34,36 and 37* is/are rejected.

7)☒ Claim(s) *3,6,7,15,16,21,22,29,32,37-39,41 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/14/09* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Examiner Initialed Interview Summary.

DETAILED ACTION

1. Claims 3, 6, 7, 14-16, 19-22, 24-27, 29, 32, 34, 36-39, 41, and 43-53 are all the pending claims for this application.

2. Claims 8, 31, 35, 40, and 42 were cancelled, Claims 14, 16, and 32 were amended and new Claims 47-53 were added in the Response of 4/6/09.

3. Claims 19, 20, 24-27 and 43-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

Newly submitted claims 48-53 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The elected claims are drawn to an anti-glypican 3 antibody and new Claims 48-53 are drawn to methods of administering the anti-glypican 3 antibody to mediate an effect.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 48-53 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. The examiner gratefully acknowledges the telephone interview with Applicants representative, Ryan McQuade, on June 16, 2009 in order to advance the prosecution towards allowance. The interview summary from June 16, 2009 is attached hereto. Mr. McQuade reported on the morning of June 19, 2009 that he did not timely receive client instructions to proceed with the examiner's proposed amendments to the claims. Accordingly, the examiner agreed to make the instant Office Action non-final in order to

address those issues discussed during the interview of June 16, 2009, and subsequently identified by the examiner.

5. Claims 3, 6, 7, 14-16, 21, 22, 29, 32, 34, 36-39, 41, and 47 are all the pending claims under examination.

6. The finality of the Office Action is withdrawn. This Office Action contains new grounds for objection and rejection.

Information Disclosure Statement

7. Applicants comments on p. 10 of the Response of 4/6/09 to explain their understanding of the examiners rational for reference #1 having been stricken on the 1449 form from the IDS of 9/29/08 are acknowledged.

8. The IDS of 5/14/09 has been considered and entered. The initialed and signed 1449 form is attached.

Withdrawal of Objections

Drawings

9. The objection to the corrected drawing figure(s) for Figures 1-20 filed on 9/29/08, because applicant did not submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version is withdrawn.

As discussed with Mr. McQuade in the telephone interview of 3/31/09 and memorialized in the interview summary of 4/8/09, the examiner agreed to withdraw the objection based on the explanation of the changes in the Response of 9/29/08.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

10. The rejection of Claim 8 for the recitation "wherein one amino acid residue substituted, deleted, added, or inserted among the heavy chain CDRs and light chain CDRs taken together" is moot for the cancelled claim.

Applicants' comments on p. 11 of the Response of 4/6/09 are acknowledged.

Claim Rejections - 35 USC § 112, first paragraph

Enablement

11. The rejection of Claims 31, 35, 40 and 42 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for an anti-glypican 3 antibody comprising mixing any light chain or VL domain from a given parent anti-glypican 3 antibody with any heavy chain or VH domain from another anti-glypican 3 antibody; or any of the anti-glypican 3 antibodies (e.g., GC33, M11F1, M3B8, GC199, GC202, GC179, GC194(2), M13B3, L9G11, M6B1, M5B9, M10D2) comprising any amino acid substitution, deletion, addition and/or insertion is moot for the cancelled claims.

Claim Rejections - 35 USC § 102

12. The rejection of Claims 14, 16 and (new Claims 36 and 38) under 35 U.S.C. 102(b) as being anticipated by Gonzalez et al. (J. Cell Biol. 141:1407-1414 (1998); cited in the IDS of 12/10/07) is withdrawn.

Applicants' amendment of Claims 14 and 16 to introduce the limitation for "monoclonal antibody" in addition to their comments on p. 12 of the Response of 4/6/09 is found persuasive.

13. The rejection of Claims 14, 16 and (new Claims 36 and 38) under 35 U.S.C. 102(b) as being anticipated by Pilia et al. (Nature Genetics 12:241-247 (1996); cited in the IDS of 12/10/07) is withdrawn.

Applicants' amendment of Claims 14 and 16 to introduce the limitation for "monoclonal antibody" in addition to their comments on p. 12 of the Response of 4/6/09 is found persuasive.

14. The rejection of Claims 14-16, 32, 34, 36-38 and 41 under 35 U.S.C. 102(a) as being anticipated by Aburatani et al. (EP1411118; published 4/21/04; filed 6/21/02; cited in the IDS of 12/10/07) is withdrawn.

Applicants' amendment of Claims 14 and 16 to introduce the limitation for "monoclonal antibody" in addition to their comments on p. 12 of the Response of 4/6/09 is found persuasive.

15. Claims 14-16, 32, 34, 36-38 and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Aburatani et al. (WO 2004/022739; published 3/18/04; filed 9/4/02; cited in the IDS of 12/10/07; English language translation equivalent attached as EP 1541680; published 6/15/05; filed 4/9/03) is withdrawn.

Applicants' amendment of Claims 14 and 16 to introduce the limitation for "monoclonal antibody" in addition to their comments on p. 12 of the Response of 4/6/09 is found persuasive.

Rejections Maintained

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. The provisional rejection of Claims 14 and 15 (and 34, 36 and 37) on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9 and 23-29 of copending Application No. 10/526,741 ("'741"; US 20060167232; filed 9/4/02; cited in the IDS of 12/10/07) is maintained, and further in view of Wichert et al. (Oncogene 2004 Jan 29;23(4):945-55).

Applicants request to hold the rejection in abeyance until further disposition of the claims on p. 12 of the Response of 4/6/09 is acknowledged, and their response is incomplete and the rejection is maintained.

As discussed during the interview of June 16, 2009, Claim 34 would be joined under the rejection. Claim 34 is dependent on Claim 14 and describes the antibody as binding to a peptide and which can be separated by SDS-PAGE under reducing conditions as analyzed by Western blotting. Wichert teaches expressing and separating the GPC3 protein on an SDS-PAGE gel and analyzed by western blotting, and where it would have been obvious to use the anti-GPC3 antibody of '741 binding to epitopes in the C-terminal domain of the protein.

Upon further consideration, the Examiner has joined Claims 36 and 37 under this rejection where a pharmaceutical composition comprising the antibody of '741 would have been obvious, more especially, where '741 claims the antibody having various biological properties, and which would otherwise be required to be in pharmaceutical format to have these properties on a cell in vitro.

New Grounds for Objection

Claim Objections

17. Claims 3, 6, 7, 15, 16, 21, 22, 29, 32, 37-39, 41 and 47 are drawn to or encompass the GC33 antibody and variants thereof, but fail to identify the antigen molecule for the antibody. Introducing “glypcan 3” into a) the preamble of Claims 3, 6, and 29 to recite, for example, "an anti-glypican 3 antibody", or b) inserting a concluding wherein clause, for example, ", wherein the antibody binds glypican 3” could overcome the objection. Amending Claim 16 to recite "an epitope of glypican 3" in line 1 could overcome the objection.

New Grounds for Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

18. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 34 in depending from Claim 14 is interpreted as being drawn a monoclonal antibody that *binds* to a peptide consisting of the sequence of the amino acid residues

546 - 551 of glypican 3 as well as to any peptide separated by SDS-PAGE under reducing conditions as analyzed by Western blotting. Claim 34 does not identify the peptide. The specification teaches the GC33 antibody binds the peptide of amino acid residues 546 - 551 of glypican 3 but does not support the GC33 antibody or any of the isolated variants being capable of binding to *any peptide* separated by SDS-PAGE under reducing conditions as analyzed by Western blotting. The claims encompass cross-reactive antibodies with any peptide which are not supported by the claims or the specification.

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials 3/29/08), the claimed invention must meet the following criteria: a) Actual reduction to practice; b) Disclosure of drawings or structural chemical formulas; c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function; d) Method of making the claimed invention; e) Level of skill and knowledge in the art; and f) Predictability in the Art.

It is noted that the term “specific binding” is not used in the immunological arts to connote exclusive binding. “Specifically binds” is not art-defined as exclusive binding as evidenced by Bost et al. (Immunol. Invest. (1988) 17:577-586) and Bendayan (J. Histochem. Cytochem. (1995) 43:881-886). That an antibody "cross-reacts", i.e., binds to more than one protein sequence does not mean that the antibody does not "specifically react" or "specifically bind" with both proteins. For example, Bost et al.

describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies that bound either the HIV or IL-2 derived sequence, did not cross react with irrelevant peptides (e.g., "Results, page 579). Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). See also USPN 6,210,670 (Berg) “Cross-Reacting Monoclonal Antibodies Specific for E-Selectin and P-selectin".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claims 14, 15, 34, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lage et al. (Virchows Arch 2001 438:567-573, cited in the IDS of 12/10/07) in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856).

Claims 14, 15, and 34 are interpreted as being drawn to an isolated monoclonal antibody capable of binding to a peptide consisting of the sequence of the amino acid residues 546 - 551 of glypican 3 (Claim 14), where the antibody is a humanized antibody (Claim 15), where the antibody binds a peptide separated by SDS-PAGE under reducing conditions as analyzed by Western blotting (Claim 34).

Claims 36 and 37 are interpreted as being drawn to a pharmaceutical composition comprising the antibody of Claim 14 or Claim 15.

The claimed monoclonal antibodies and pharmaceutical compositions were prima facie obvious at the time of the invention over Lage and Steplewski.

Lage et al. teach the production of a monoclonal antibody to GPC3 using an oligopeptide of amino acids 537-556 of human GPC3, see Materials and Methods. Lage et al. use the standard art technique of fusing spleen cells from immunized mice with myeloma cells to generate hybridomas for the production of the monoclonal

antibody, which leads to recombination of the fused cellular genomes, thus the monoclonal antibodies are recombinant antibodies. Lage teach western-blot analysis of the monoclonal antibody recognizing the peptide for GPC3 separated and isolated on SDS-PAGE gels (Fig. 1).

Lage et al. does not teach a humanized form of the antibody or pharmaceutical compositions of a wild-type antibody of humanized antibody.

Steplewski et al. teach that mouse monoclonal antibodies are humanized to overcome the problem of short half-life and immunogenicity of murine monoclonal antibodies in humans, see page 4852, first paragraph. Steplewski et al. teach the generation of humanized mouse monoclonal anti-bodies using Cγ1, Cγ2, Cγ3, and Cγ4 human heavy chains and human Cκ light chains, see Materials and Methods.
Steplewski

It would be *prime facie* obvious to one of skill in the art at the time the invention was made to humanize the monoclonal antibody of Lage et al. using the methods of Steplewski et al. to make humanized monoclonal antibodies that have Cγ1, Cγ2, Cγ3, or Cγ4 human heavy chains and human Cκ light chains and creating pharmaceutical compositions comprising the antibodies because Steplewski et al. teach that humanization of antibodies is done to overcome the problems of using mouse monoclonal antibodies in human therapy. One would have been motivated to humanize antibodies the monoclonal antibody of Lage et al. for potential therapeutic antibodies One of skill in the art would have had a reasonable expectation of success of making a humanized, monoclonal antibody against a peptide consisting of amino acid residues of

546-551 of GPC3 given that the monoclonal antibody of Lage et al. binds within amino acid residues 375-580 of GPC3, the methods for humanizing antibodies were well known in the art at the time the invention was made. Adjusting the amino acid residues for this overlapping region of the GPC3 protein would have been within the skill of the ordinary artisan at the time of the invention.

A prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties." Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)); "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. Id. See also In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08) (See MPEP 2144.05).

Conclusion

20. No claims are allowed.

21. The GC33 antibody and VH/VL variants thereof are free of prior art.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority